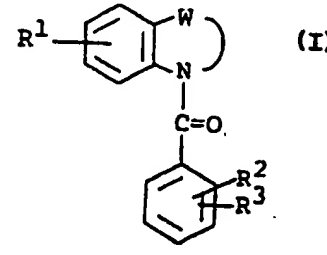
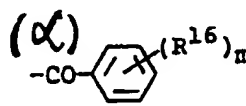


PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁵ : A61K 31/00, C07D 215/08 C07D 215/12, 223/16, 225/06 C07D 241/42, 243/14, 265/36 C07D 267/14</p>	A1	<p>(11) International Publication Number: WO 91/05549</p> <p>(43) International Publication Date: 2 May 1991 (02.05.91)</p>												
<p>(21) International Application Number: PCT/JP90/01340</p> <p>(22) International Filing Date: 18 October 1990 (18.10.90)</p> <p>(30) Priority data:</p> <table border="0"> <tr> <td>1/274338</td> <td>20 October 1989 (20.10.89)</td> <td>JP</td> </tr> <tr> <td>2/66063</td> <td>15 March 1990 (15.03.90)</td> <td>JP</td> </tr> <tr> <td>2/105580</td> <td>20 April 1990 (20.04.90)</td> <td>JP</td> </tr> <tr> <td>2/181858</td> <td>9 July 1990 (09.07.90)</td> <td>JP</td> </tr> </table> <p>(71) Applicant (for all designated States except US): OTSUKA PHARMACEUTICAL COMPANY, LIMITED (JP/JP); 9, Kandatsukasa-cho 2-chome, Chiyoda-ku, Tokyo 101 (JP).</p> <p>(72) Inventors; and</p> <p>(73) Inventors/Applicants (for US only): OGAWA, Hidenori (JP/JP); MIYAMOTO, Hisashi (JP/JP); 21-3, Yoshinari-Aza-Todoroki, Ojin-cho, Tokushima-shi, Tokushima 771-11 (JP). KONDO, Kazumi (JP/JP); 19-27, Okuwajima-Aza-Suberiwahama, Muya-cho, Naruto-shi, Tokushima 772 (JP). YAMASHITA, Hiroshi (JP/JP); 57-1, Sasakino-Aza-Hachikami, Matsushige-cho, Itano-gun, Tokushima 771-02 (JP). NAKAYA, Kenji (JP/JP); 48, Kamibetsukukita, Kawauchi-cho, Tokushima-shi, Tokushima 771-01 (JP). KOMATSU, Hajime (JP/JP); TANAKA, Michinori (JP/JP); KORA, Shinya (JP/JP); 463-10, Kagasuno, Kawauchi-cho, Tokushima-shi, Tokushima 771-01 (JP). TOMINAGA, Michiaki (JP/JP);</p>		1/274338	20 October 1989 (20.10.89)	JP	2/66063	15 March 1990 (15.03.90)	JP	2/105580	20 April 1990 (20.04.90)	JP	2/181858	9 July 1990 (09.07.90)	JP	<p>310-6, Takaiso, Kamiita-cho, Itano-gun, Tokushima 771-13 (JP). YABUUCHI, Yoichi (JP/JP); 900-25, Omatsu, Kawauchi-cho, Tokushima-shi, Tokushima 771-01 (JP).</p> <p>(74) Agents: AOYAMA, Tamotsu et al.; Twin 21 Mid Tower, 1-61, Shiromi 2-chome, Chuo-ku, Osaka-shi, Osaka 540 (JP).</p> <p>(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), KR, LU (European patent), NL (European patent), SE (European patent), US.</p> <p>Published With international search report.</p>
1/274338	20 October 1989 (20.10.89)	JP												
2/66063	15 March 1990 (15.03.90)	JP												
2/105580	20 April 1990 (20.04.90)	JP												
2/181858	9 July 1990 (09.07.90)	JP												
<p>(54) Title: BENZOHETEROCYCLIC COMPOUNDS</p> <div style="text-align: center;">  <p>(I)</p> </div> <div style="text-align: center;">  <p>(α)</p> </div> <p>(57) Abstract</p> <p>Novel benzoheterocyclic compounds of formula (I), wherein R¹ is H, halogen, alkyl, optionally substituted amino, alkoxy; R² is H, halogen, alkoxy, phenylalkoxy, OH, alkyl, optionally substituted amino, carbamoyl-alkoxy, optionally substituted amino-alkoxy, optionally substituted benzoyloxy; R³ is a group: -NR⁴R⁵ or -CO-NR¹¹R¹²; R⁴ is H, optionally substituted benzoyl, alkyl; R⁵ is a group α [R¹⁶ is halogen, optionally substituted alkyl, OH, alkoxy, alkanoyloxy, alkylthio, alkanoyl, carboxy, alkoxy-carbonyl, CN, NO₂, optionally substituted amino, phenyl, cycloalkyl, etc., or a group: -O-A-NR⁶R⁷; m is 0 to 3], phenyl-alkoxycarbonyl, alkanoyl, phenyl-alkanoyl, etc.; R¹¹ is H or alkyl; R¹² is cycloalkyl or optionally substituted phenyl; and W is a group: -(CH₂)_p (p is 3 to 5) or -CH=CH-(CH₂)_q (q is 1 to 3), the carbon atom of these groups being optionally replaced by O, S, SO, SO₂ or a group: -N(R¹³)- and further these groups having optionally 1 to 3 substituents of alkyl, alkoxy-carbonyl, carboxy, OH, O, alkanoyloxy, etc., which have excellent vasopressin antagonistic activities and are useful as vasodilator, hypotensive agent, water diuretics, platelet agglutination inhibitor, and a vasopressin antagonistic composition containing the compound as the active ingredient.</p>														

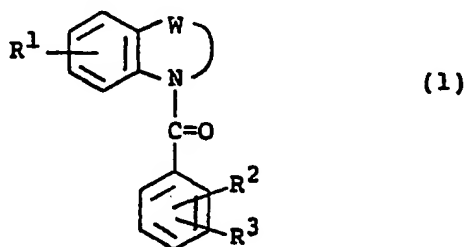
BEST AVAILABLE COPY

BENZOHETEROCYCLIC COMPOUNDSTechnical Field

This invention relates to novel benzoheterocyclic compounds which have excellent vasopressin antagonistic activities and are useful as vasodilator, hypotensive agent, water diuretics, platelet aggregation inhibitor.

Disclosure of the Invention

The benzoheterocyclic compounds of this invention have the following formula:



wherein R^1 is hydrogen atom, a halogen atom, a lower alkyl, an amino having optionally a lower alkyl substituent, or a lower alkoxy,

R^2 is hydrogen atom, a halogen atom, a lower alkoxy, a phenyl(lower)alkoxy, hydroxy, a lower alkyl, an amino having optionally a lower alkyl substituent, a carbamoyl-substituted lower alkoxy, an amino-substituted lower alkoxy having optionally a lower alkyl substituent, or a benzyloxy which has optionally a halogen substituent on the phenyl ring,

R^3 is a group of the formula: $\begin{matrix} R^4 \\ \diagup \\ -N \\ \diagdown \\ R^5 \end{matrix}$ or a group of

the formula: $\begin{matrix} O \\ || \\ -C-N \\ \diagup \quad \diagdown \\ R^{11} \quad R^{12} \end{matrix}$,

BEST AVAILABLE COPY

are the same or different and are each hydrogen atom, a lower alkyl, a lower alkenyl, a lower alkanoyl, a cycloalkyl, an oxiranyl-substituted lower alkyl, a lower alkyl having optionally 1 to 2 substituents selected from a lower alkoxy, hydroxy and an amino having optionally a lower alkyl substituent, a phenyl-lower alkyl, a pyridyl-lower alkyl, a lower alkylsulfonyl, benzoyl, a lower alkoxy-carbonyl, anilinocarbonyl, an aminocarbonyl having optionally a lower alkyl substituent, a cyano-substituted lower alkyl, a lower alkoxycarbonyl-substituted lower alkyl, a carbamoyl-substituted lower alkyl, a carboxy-substituted lower alkyl, a tetrahydropyranyloxy-substituted lower alkyl, a lower alkanoyloxy-substituted lower alkyl, a piperidinyl having optionally a phenyl-lower alkyl substituent on the piperidinyl ring, a halogen-substituted lower alkanoyl, an imidazolyl-substituted lower alkanoyl, an amino-lower alkanoyl having optionally a substituent selected from a lower alkyl and a lower alkoxycarbonyl, an aminocarbonyl-lower alkyl having optionally a lower alkyl substituent, or a phenyl-lower alkoxycarbonyl, or R^{14} and R^{15} may bind together with nitrogen atom to which they bond to form a 5- or 6-membered saturated heterocyclic group with or without being intervened with nitrogen or oxygen, wherein the heterocyclic group may optionally have a substituent selected from a lower alkyl, a phenyl-lower alkyl or a lower alkanoyl).

The benzoheterocyclic compounds of the formula (1) and

BEST AVAILABLE COPY

their salts have excellent vasopressin antagonistic activities and vasodilating activity, hypotensive activity, activity for inhibiting saccharide release in liver, activity for inhibiting growth of mesangium cells, water diuretic activity, platelet agglutination inhibitory activity and are useful as vasodilator, hypotensive agent, water diuretics, platelet agglutination inhibitor and are used for the prophylaxis and treatment of hypertension, edema, ascites, heart failure, renal function disorder, vasopressin parasecretion syndrome (SIADH), hepatocirrhosis, hyponatremia, hypokaliemia, diabetic, circulation disorder, and the like.

Each group in the above formula (1) includes specifically the following groups.

The "lower alkoxy" includes a straight chain or branched chain alkoxy group having 1 to 6 carbon atoms, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy, and the like.

The "lower alkyl" includes a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl, and the like.

The "halogen atom" includes fluorine atom, chlorine atom, bromine atom and iodine atom.

The "amino having optionally a lower alkyl substituent" includes an amino having optionally one or two substituents selected from a straight chain or branched chain alkyl group having 1 to 6 carbon atoms, for example, amino,

BEST AVAILABLE COPY

WO 91/05549

- 130 -

PCT/JP90/01340

(propylene glycol), ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, polyoxyethylene sorbitan fatty acid esters, and the like. In this case, the pharmaceutical preparations may also be incorporated with sodium chloride, glucose, or glycerin in an amount sufficient to make them isotonic, and may also be incorporated with conventional solubilizers, buffers, anesthetizing agents. Besides, the pharmaceutical preparations may optionally be incorporated with coloring agents, preservatives, perfumes, flavors, sweetening agents, and other medicaments, if required.

The amount of the active compound of this invention (active ingredient) to be incorporated into the anti-vasopressin preparations is not specified but may be selected from a broad range, but usually, it is preferably in the range of 1 to 70 % by weight, more preferably 5 to 50 % by weight.

The anti-vasopressin preparation of this invention may be administered in any method, and suitable method for administration may be determined in accordance with various forms of preparation, ages, sexes and other conditions of the patients, the degree of severity of diseases, and the like. For instance, tablets, pills, solutions, suspensions, emulsions, granules and capsules are administered orally. The injections are intravenously administered alone or together with a conventional auxiliary liquid (e.g. glucose, amino acid solutions), and further are optionally administered alone in intramuscular, intracutaneous, subcutaneous, or intraperitoneal route, if required. Suppositories are

BEST AVAILABLE COPY

administered in intrarectal route.

The dosage of the anti-vasopressin agent of this invention may be selected in accordance with the usage, ages, sexes and other conditions of the patients, the degree of severity of the diseases, and the like, but is usually in the range of about 0.6 to 50 mg of the active compound of this invention per 1 kg of body weight of the patient per day. The active compound is preferably contained in an amount of 10 to 1000 mg per the dosage unit.

Brief Description of Drawing

Fig. 1 to Fig. 4 show a chart of NMR (CDCl_3) of the compounds in Examples 978 and 979.

Best Mode for Carrying Out the Invention

The present invention is illustrated by the following Preparations of anti-vasopressin agent, Reference Examples of processes for preparing the starting compounds to be used for preparing the active compounds, Examples of processes for preparing the active compounds, and Experiments of the activities of the active compounds of this invention.

Preparation 1

Film coated tablets are prepared from the following components.

<u>Components</u>	<u>Amount</u>
4-Methylamino-1-[4-(3,5-dichlorobenzoyl-amino)benzoyl]-1,2,3,4-tetrahydroquinoline	150 g

BEST AVAILABLE COPY

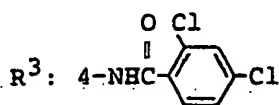
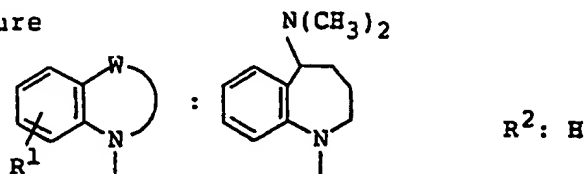
WO 91/05549

- 374 -

PCT/JP90/01340

Example 407

Structure



Crystalline form: White powder

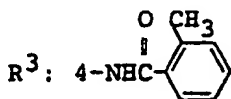
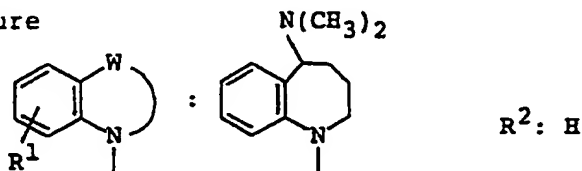
Recrystallization solvent: Ethanol

Melting Point: 181 - 183°C

Form: Free

Example 408

Structure



Crystalline form: White powder

Recrystallization solvent: Ethanol

Melting Point: 207 - 208°C

Form: Free

BEST AVAILABLE COPY